A systematic review and meta-analysis of prospective transition from major depression to bipolar disorder

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Abstract

Objective: Some people with major depressive disorder (MDD) may be at a pre-onset stage for Bipolar Disorder (BD), where early identification or prevention efforts may be feasible. We aimed to identify rates and characteristics predictive of transition to BD in prospective follow-up studies of people with MDD.

Methods: Using a systematic search strategy, we identified studies with a diagnostic ascertainment of MDD and BD of an adequate standard, and where the minimum length of follow-up was 6 months. We examined the incidence and point prevalence of BD and the pooled odds ratios (*OR*) for baseline predictors.

Results: From 5554 unique publications, 56 were included. Nearly a quarter of adults (22.5%) and adolescents with MDD and followed up for a mean length of 12-18 years developed BD, with the greatest risk of transition being in the first 5 years. The meta-analysis identified that transition from MDD to BD was predicted by family history of BD (*OR*=2.89, 95%CI:2.01-4.14, *N*=7), earlier age of onset of depression (*g*= -0.33, *SE*=0.05, *N*=6), and presence of psychotic symptoms (*OR*= 4.76, 95%CI:1.79-12.66, *N*=5).

Conclusion: Participants with the identified risk factors merit closer observation and may benefit from prevention efforts, especially if outcomes broader than BD are considered.

Keywords: bipolar disorder, depression, meta-analysis, risk factors, affective disorders.

Summations

1. Nearly a quarter of MDD cases followed up for more than 12 years transitioned to BD, with the greatest risk in the first 5 years of follow-up.
2. Consistent predictors of transition were a lower age of MDD onset, family history of BD, and presence of psychotic symptoms in meta-analysis and subthreshold manic symptoms, in qualitative synthesis.
3. Use of samples with MDD enriched using such a profile may help identify sub-groups where preventive interventions may be feasible, especially if outcomes broader than bipolar disorder are considered.

Considerations

1. The quality of included studies were highly variable and this may contribute to bias
2. Clinical and statistical heterogeneity limited meta-analysis of some risk factors

3. Future cohort studies that have adequate statistical power to examine these risk factors may be necessary to clarify the relative predictive validity of risk factors, in terms of independence, additive effects, and/or magnitude of effect.

Introduction

Early intervention may help to reduce the impact of bipolar disorder (BD) (1). To achieve this, preventative efforts first require the identification of individuals at highest risk of onset of mania or hypomania. There are several potential high risk states, including where a person has: (i) a family history of BD (2); (ii) sub-threshold mood symptoms (3, 4); or (iii) major depression disorder (MDD) (3). From the perspective of prevention of BD, family history and subthreshold mood symptoms have been relatively well studied, while people with MDD have not been a major target of early identification efforts. Targeting MDD may hold some advantages compared to the other risk states. First, most people with BD (58-71%) have depressive onset polarity (5). Second, MDD may represent a more proximal risk state for BD. For example, asymptomatic familial at-risk cohorts need to be followed up for significant lengths of time to allow for sufficient transitions (6). Thus, a key pragmatic question for early intervention is whether the likelihood of transition to BD from MDD occurs at a sufficient rate to justify screening and intervention. Additionally, factors that help improve the identification of those with a greater likelihood of transition to BD may be of direct relevance to clinicians providing care for people presenting with major depressive episodes.

While previous reviews have examined the development of BD in samples with depression, these have been unsystematic (7), limited to antidepressant associated switch (8) or in samples under the age of 18 (9). Importantly, variability in follow-up periods has not always been considered and is likely to impact on transition rate estimates. Thus, the *aims of the study* were to examine: (i) how likely transition was from MDD to BD; (ii) whether there was a peak risk period in which transitions occur; and (iii) whether there were distinctive profiles of individuals who transition from MDD to BD.

Methods

We examined the published literature on the rates and predictors of longitudinal transition to BD I or II among cohorts identified to have syndromal MDD at baseline that were followed up prospectively. The reporting of the systematic review conforms with the Preferred

Reporting Items for Systematic Review and Meta-Analysis (10) (PRISMA) checklist (Supplementary Table 3).

Search Strategy: We constructed two strategies and searched citations of included studies or reviews to identify all relevant publications that met eligibility criteria for the review. The primary search strategy included the following terms in title and abstracts:

1. Mood disorders: Depressive disorder, Affective Disorders, Psychotic+, Bipolar Disorder (or Bipolar and related disorders) (in full texts) along with unipolar*, depressive (disorder* OR syndrome*) MDD, (severe OR endogenous OR neurotic) (depression* OR depressive), cyclothym*, labile, hypomani*, hypermani*, manic, mania*, bipolar, BP, BD, BPI, BPII, mood, affective, paraphren*, pre-bipolar

2. Study method: The terms conversion, evolv*, cycl*, shift*, switch*, progress*, predict* , emerg*, transition*, progress*, develop*, stability

These terms were searched in Medline, PsycINFO, and Embase (using the Ovid interface) and limited to articles published from 1 January 1979 until 16 September 2016. Bibliographies of reviews and original research articles were screened for relevant materials. Please see Supporting Information (online) for a full search algorithm.

Eligibility Criteria

We included:

1. articles published in English;
2. original research;
3. studies with paediatric, adolescent, and adult samples up to the age of 65 years. Samples required a baseline diagnosis of MDD using recognized diagnostic criteria, namely the Diagnostic and Statistical Manual for Mental Disorders (3rd edition or later) or the International Classification of Diseases (10th ed.; ICD-10; World Health Organization, 2010);
4. studies where the BD I or II diagnosis was made using diagnostic criteria from the 3rd edition or later versions of the DSM (DSM-III), Research Diagnostic Criteria (RDC – 'definite' for hypomania), or ICD-10;
5. studies with a minimum follow-up of 6 months;
6. studies that reported both rates and predictors of transitions.

We excluded:

1. studies of geriatric depression to reduce risks of inclusion of secondary organic mania (11);

2. record linkage studies or studies using administrative datasets as these studies often have poorer reliability and sensitivity with regards to diagnostic ascertainment (particularly for BD II (12)) than studies where participants were individually interviewed for research purposes. Additionally, clinician diagnoses used in these registers are often significantly discordant from research diagnoses, and also differ between registries (13);

3. studies that did not report data on MDD cases separately at baseline and/or did not report the outcomes for MDD cases separately at follow-up. This included trans-diagnostic or disease-free samples recruited to prospective birth cohort studies (14) and studies of high-risk families or offspring of parents with BD (15).

Study Selection: Identified articles were initially screened independently by AR and two other researchers (from SC, MA, SH and CD) to assess eligibility. Any uncertainties regarding eligibility were resolved via consensus.

Data Extraction:

Data were extracted from included studies in a systematic manner using a pre-designed extraction form (undertaken by AR). On the proforma the following information was recorded: (i) study design; (ii) country of origin; (iii) baseline sample size; (iv) diagnostic criteria that were employed at baseline and follow-up, assessment instruments used and the person undertaking the examination; (v) treatment setting; (vi) sample attrition rate; (vii) follow-up duration and reassessment time points; (viii) blinding of assessment at follow-up; (ix) whether efforts were made to exclude BD cases at baseline; (x) baseline characteristics including age, gender, depressive phenomenology and reported comorbidities, illness course, exclusion criteria, treatment characteristics; (xi) outcome of BD (and any BD sub-types), prevalence and number of cases at follow up; and (xii) predictors identified in individual studies, statistical methods for analyses, and reported effect sizes.

We aimed to examine the following group of predictive variables:

1. *demographic features* - age and gender

2. *family history* - family history of BD, family history of affective disorders (including MDD or BD, where authors did not report the prevalence separately), presence of multi-generational family histories or a 'loaded affective pedigree'. A loaded family history was defined as the presence of 3 or more family members with a mood disorder and a multi-generational family history was defined as 3 generations of the family tree having at least one person with a mood disorder.

3. *course characteristics of MDD-* age of onset of MDD, presence of recurrent MDD (defined as the presence of more than 1 MDE), presence of chronic MDE (defined as the persistence of MDE for more than 2 years)

4. *symptom characteristics associated with baseline MDD* - presence of psychotic symptoms, presence of manic symptoms below the threshold for BD I or II, atypical symptoms of depression, and presence of specific symptoms such as guilt, irritability and somatic symptoms. Manic symptoms below the threshold of BD I or II could include BD NOS, (hypo)manic symptoms in the context of medication use (referred to as 'pharmacological hypomania'), as well as manic symptoms. Presence of psychotic symptoms could be examined only within the sub-sample of studies that did not select participants solely based on their diagnoses being one of MDD with psychosis.

5. *comorbid disorders* - presence of comorbid anxiety disorders; disruptive behaviour disorders (e.g., ADHD, conduct disorders); and personality disorders.

Heterogeneity in definition of baseline variables: To decrease clinical heterogeneity, only those variables defined in a similar manner across studies were pooled. For example, psychosis was combined with reports of 'delusions and hallucinations', but pharmacological hypomania was not combined with hypomanic symptoms. With respect to diagnostic heterogeneity, participants with baseline diagnoses of schizoaffective disorder (i.e., depressive type at baseline and manic type at follow-up) were excluded from the examination of BD rates. In line with DSM IV (16), the development of mixed episodes in cases with MDD were considered equivalent to manic episodes.

Data management of multiple outputs from individual cohorts: Data from multiple reports for the same cohorts were included provided that duplicate data were not included within any specific analysis. For example, among cohorts where rates of BD were reported at more than one follow-up time, data from each follow-up were included for quantification of rate of transition over time ensuring that data from each cohort did not appear more than once in each pooled analysis. Thus, for each pooled analysis, only independent datasets were included.

Definition of prepubertal studies: In line with previous meta-analyses (18), studies where the majority of the sample was described as prepubertal or where the mean baseline age of the sample was less than or equal to 12 years at baseline were considered to be prepubertal

studies. These were analysed separately due to the possibility that prepubertal BD may have been diagnosed differently from adult-pattern BD (16).

Variables were included in a qualitative synthesis if more than one independent publication examined any association between the variable and BD. Variables were additionally included in a quantitative synthesis if three or more independent reports examined an association between that variable and BD. Length of follow-up was used as a proxy measure of the time to the index episode of BD, as this was the most consistent information available. In quantitative analysis, mean length of follow-up was utilized when this information was directly available or could be extracted from the reported data.

Quality Assurance: Study quality was assessed using a purpose-built measure. This included items from the Newcastle Ottawa Scale (17) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (18). The instrument covered the domains of overall study design, ascertainment of diagnoses, representativeness of the depressed sample at baseline, blinding on follow-up assessment, the rate of attrition of the sample and the risk of inclusion of subthreshold BD on follow-up (details in Supplementary Table 2).

Statistical Analyses: Analyses were conducted separately for prepubertal samples, and for adolescent and adult samples (the latter two groups were combined) using random effects models from the Comprehensive Meta-Analysis v2.0. The main outcomes for the meta-analytic component of the review were:

1. incidence of BD I or II expressed in events per 100 person years of follow-up; and
2. point prevalence of BD I or II expressed as a percentage;
3. pooled odds ratio (*OR*) with 95% confidence intervals (95% CI) for predictors of transition to BD I or II – we used the reported *OR* or estimated them from prevalence data reported in studies.

Publication bias was examined by visual inspection of a funnel plot of logit event rate (prevalence of BD on follow-up) mapped against study precision and Egger's regression.

Analyses of rates and predictors:

Incidence: Within the first two years, incidence of BD in 100 person-years of follow-up was estimated. The person-years of follow-up were calculated by multiplying the mean duration of follow-up (in years) with the mean-population (number of persons) at risk during this

period (19). The latter was derived using the intake sample size, the follow-up sample size and the transitions to BD during this time. This method was not used for analyses of later follow-ups due to the lack of adequate data on sample attrition compared to transition at various time points.

Point prevalence: Beyond the two-year follow-up point, transitions to BD were estimated as the point prevalence based on the identified number of persons who developed BD and the persons with MDD who were followed up to that time point (i.e., in the retained sample not the original sample).

Examination of the variance in point prevalence: Given the possible relationship between prevalence of BD and length of follow-up, and in the absence of survival analyses or individual patient data from the studies, prevalence rates were sub-grouped based on: (i) measures of central tendency including mean, median and mode; (ii) a visual examination of a scatterplot of the length of follow-up compared with point prevalence of BD at that length of follow-up (meta-regression); and (iii) percentile distribution of the length of follow-up in all post-pubertal studies (dividing studies into quartiles). The point prevalence was used to arrive at an approximate estimate of the prevalence of BD per year of follow-up (by dividing the prevalence at each time point by the length of years of follow-up). For examination of the variance in the transition rate over time, this prevalence rate per year of follow-up was correlated with the length of follow-up in years, using Spearman's rank correlation. This method was limited to examination of the variation of rates of transitions over time only, as this estimation does not account for the person-years followed up in each study and the variability over time. When the effect of length of follow-up on the point prevalence of BD could be minimized, subgroup analyses using moderators were conducted in order to examine for effects of categorical variables (such as recruitment of samples) describing groups of studies. Meta-regressions were utilized to examine for residual heterogeneity related to continuous variables such as age, gender distribution and study quality.

Analysis of predictors of transition to BD: Pooled ORs were estimated from prevalence of transition to BD in groups with or without the variable present, or when this was not available, then from univariate *OR*s reported in the papers or available in communication with the authors. Subgroup analyses and meta-regressions were not possible as few predictors had sufficient studies in analyses of pooled *OR*s.

Examination of heterogeneity: Statistical heterogeneity was tested using I^2 values (20). I^2 is the ratio of true heterogeneity to the total variance observed across the observed effect

estimates (21). Random effects analyses were used uniformly in all analyses due to the expectation of large clinical heterogeneity in the included studies due to which the assumptions of fixed effects were not considered to be met. Random effects analyses were also more likely to minimize the impact of very large or very small studies. When the I^2 values were moderate or high (defined as >25%) (20) using random effects models, the data were not pooled (21). Alternately, sensitivity analyses were conducted by excluding individual studies to examine models with lower statistical heterogeneity.

Results

---Insert Fig 1 about here---

Included studies

Of 5554 unique publications, full texts of 188 articles were screened and 56 of those met eligibility criteria (Figure 1). All studies provided qualitative data (Supplementary Table 1), while 35 were utilized for the analysis of rates of transition from MDD to BD, and 24 studies were included in qualitative or quantitative synthesis of predictors. Studies varied substantially in their design and quality (Supplementary Table 2). Most studies examined cohorts with MDD for a variety of outcomes and examined BD outcomes in post-hoc case-control designs. This meant that a) either all risk factors were not measured or b) studies were not powered to examine the baseline risk factors for their ability to predict transition to BD in univariate or multivariate models. There was no evidence of publication bias in a funnel plot of logit event rate plotted against study precision (Supplementary Figure 1) or according to Egger's test. The mean or median length of follow-up varied from 8 months to 18 years. The modal duration was 2 years and the mean length of follow-up was 5.87 years.

Studies with adolescent and adult depression

<u>Rates of transition to BD from meta-analysis</u>

1) Incidence of BD within 2 years of follow-up (Fig 2):

The cumulative incidence of BD was 4.0 per 100 person-years of follow-up (*SE*=0.5, *Q*=10.5, *df*=10, I^2=4.42) (Figure 2) (N=11). One study was excluded because it added high statistical and clinical heterogeneity (22). This is reflected in the study's protocol that required multiple structured diagnostic assessments over a 12-month period and in the findings that 22.5% of those with unipolar MDD were re-diagnosed as BD II over this time and 11.8% of those with an initial diagnosis of BD II were re-diagnosed as having MDD over the 12-month period.

---Insert Fig 2 about here---

2) Rates of transition over time

---Insert Fig 3 about here---

A random-effects meta-regression of the length of follow-up on rate of transition to BD indicated a significant positive relationship (Slope=0.062, *SE*=0.03, *Q*=4.33, *df*= 1, *p*=0.038, T^2=0.62). The scatterplot revealed a cluster of studies with follow-ups of (i) up to 2 years; (ii) between 2 and 6 years; (iii) between 6 and 12 years; and (iv) more than 12 years (Figure 3). The prevalence of transition to BD in studies with 12 to 18 years of mean follow-up was 22.5% (95% CI: 15.8-31.1), and sub-group analysis indicated that studies with length of follow-up greater than 12 years had a significantly greater point prevalence (proportion) of BD [Supplementary Figure 2]. However, these studies did not differ in their point prevalence of BD when divided into subgroups at cut-points (2.0 y, 4.0 y, 10.0 y) based on quartiles in sensitivity analyses. Please see Supplementary Figure 5 and footnotes for details of further examination of residual heterogeneity in the point prevalence of BD. The prevalence rate per year of follow-up was strongly negatively correlated with the length of follow-up (r_s=-0.57, *p*<0.001, *N*=35), and this result remained after excluding one outlier study in the early years of follow-up (r_s=-0.54, *p*<0.001, *N*=34) in sensitivity analysis [Supplementary Figure 3].

Findings from qualitative synthesis of rates:

In the largest study with multiple follow-ups (21), the majority of transitions to BD II or BD I occurred in the first 4 and 8 years respectively. A further publication from the same dataset (22) indicated that the rate of transition to BD was 2.5% cases per year in the first 5 years and showed a rate of transition thereafter of approximately 0.5% per year. In the Zurich study (23) and the Iowa 500 study (24), over 85% of transitions from MDD to BD occurred within 3-5 years of prospective follow-up.

Baseline predictors associated with transition to BD in meta-analysis:
A) Gender
Ten reports provided data on gender distribution, while seven provided homogeneous data that allowed meta-analysis. The *OR* for transition to BD was non-significantly lower in females (*OR*=0.74; 95% CI of OR 0.48-1.13, Q= 5.84, Q*df*= 6, I^2=0) (Figure 4); but only one study reported a significant association between male gender and transition (25).

---Insert Fig 4 about here---

B) Age of onset of depression

Nine articles examined the association between age of onset of MDD and transition to BD (25-34). All studies except two (31, 34) identified a significant association between lower age of onset and higher rates of transition. Data from five articles were combined in a meta-analysis and the pooled Hedges *g* of -0.32 (*SE*=0.05, *Q*=5.90, *df*= 5, I^2=15.3%) indicated a small-medium effect (Figure 5). Age at onset of MDD in cases that did develop BD was 4.8 years (*SE*=0.52) earlier than age at onset of MDD in those who did not develop BD.

---Insert Fig 5 about here---

C) Family history variables

Among eight studies (25, 29, 31, 35-39), five identified a positive association between family history of BD and onset of BD, with a pooled *OR* of 2.89 (95% CI: 2.17-4.14) (Figure 4).

Four studies (25, 28, 40, 41) examined the association between a family history of affective disorders (MDD or BD) and transition to BD (Figure 4); one reported a significant association (25). At the same time, three studies and their pooled *OR* failed to identify a significant association between family history of depression in the index cases and transition to BD (31, 34, 42).

D) Presence of psychotic symptoms

Four of five studies reported a significant association between psychotic symptoms and later onset of BD (29, 32, 35, 36, 43), with a pooled *OR* of 4.76 (95% CI of *OR*: 1.79-12.66, *Q*=5.23, *df*=4, I^2= 23.5) (Figure 4).

E) Antidepressant use

Meta-analysis of data from four studies demonstrated a non-significant association [*OR*=1.5 (95% CI of *OR*: 0.68-3.48)] between antidepressant use and transition to BD (29, 38, 44, 45).

Baseline predictors of transition based on qualitative data

A) Phenomenology and course of depression

Severity of depression (30, 35), guilt (35, 46, 47), and mood lability (48, 49) coexistent with baseline MDD were associated with BD in two or three studies each. The relationship between recurrent MDD was inconsistent with studies identifying a significant association

(25, 30, 33, 50) and others failing to do so (34, 42). The difference in reporting prevented meta-analysis. Suicidal ideation (28, 47), or attempts (25, 28, 31) did not consistently predict transition. Chronicity of depression (≥2 years) (32, 36) and atypical features were inconsistently related to the transition to BD. One study (26) identified an association with 'hypersomnic-retarded' depression while later studies did not identify this association, in multivariate (34, 47, 51) or univariate (35, 42) analysis.

B) Subthreshold (hypo)manic features

The presence of subthreshold hypomanic symptoms (34, 42, 48) was associated with BD transition. The total number of baseline manic symptoms was predictive of later BD in two studies that also identified a dose-response relationship between the number of manic symptoms and transition to BD (34, 42). Antidepressant associated subthreshold hypomanic periods were associated with greater odds of transition in two studies (26, 52).

C) Other comorbid disorders and symptoms

Comorbid social phobia was associated with transition to BD in two multivariate analyses (33, 53), while the relationship between substance use disorders (25, 28, 33, 47) as well as generalized anxiety (33, 53) or anxiety disorders as a group (34, 47) and BD transition were inconsistent.

D) Other family history variables

Two studies (35, 36) identified significant associations between risk of developing BD and either a loaded family pedigree (with multiple affected family members) or family history of affective disorders spanning three generations.

E) Other risk factors

Child abuse (51) and the severity of childhood trauma (34) were associated with later transition to BD in multivariate analyses in two studies.

Prevalence and predictors in prepubertal samples

The cumulative transition rate to BD in four studies, with follow-ups ranging from 6 to 12 years, was 19.5% (95% CI of *OR*: 7.4- 42.2, *Q*=3.08, *df*=3, I^2=2.6) (Supplementary Fig 4). Within prepubertal samples (54-58), the predictors of transition included family history (56), subthreshold BD (59) and comorbid disorders, such as ADHD (58).

Discussion

Our meta-analysis identified that four persons out of every 100 with MDD followed up for each year are likely to transition to BD in the first two years. Almost a quarter of those followed up for more than 12 years transitioned to BD. Qualitative synthesis suggested that the greatest risk of transition from MDD to BD is in the first 5 years after baseline assessment, and meta-analysis confirmed the finding of greater transitions in the early years of follow-up. The most consistent predictors of diagnostic change among post-pubertal samples with MDD in meta-analytic examination were family history of BD, earlier age of onset and presence of psychotic symptoms. Additionally, qualitative results suggested that subthreshold manic symptoms may be predictive of transition to BD.

Rates of transition: Within the first two years, the incidence of BD was many-times higher among samples with MDD compared with the general population (estimated to be 0.73 per 100 person years of follow-up) (60). Thus, MDD can be a precursor stage for BD, and could help identify persons at risk of mania or hypomania, especially in the early years of follow-up. Factors accounting for the increased transition rate in the first few years may include more intensive follow-up, greater participant retention, as well as pathogenic processes that first account for the depressive episode but continue to operate to produce a first episode of mania or hypomania shortly afterwards.

Predictors of transition: Family history of BD was one of the most commonly identified risk factors. The relationship between transition and family history of mood disorders may be confounded by two studies where the family history of BD may have increased the risk of transition (25, 35). The lack of relationship between a family history of depression and later BD indicates the relative specificity of family history of BD to predicting later BD in MDD samples. This is consistent with family history studies that have identified specificity in familial transmission of mania and depression (61). Identified predictive factors such as age of onset, psychotic symptoms, and recurrent MDD may represent independent vulnerabilities or subtypes of depression with greater disorder severity. Two studies (35, 53) identified a direct association between depression severity and later BD.

Antidepressant use without associated hypomania was not related to a greater risk of transition in our meta-analysis, potentially moderated by the impact of mood stabilizers. In one study (44), the group that later developed (hypo)mania was more likely to be taking mood-stabilizers even prior to their first (hypo)manic episode. Overall, the exclusion of short-term follow-up studies (<6 months) may have limited our ability to examine the risk of antidepressant associated mood switch.

Limitations

The main limitation of the meta-analysis is quality of the included studies. Nearly all studies were case-control in design and there was substantial methodological and clinical heterogeneity with respect to cohort characteristics such as study design and sample size. This heterogeneity resulted in only a small number of studies contributing to predictor analyses, limiting the precision of the estimates of effect size for each predictor. Heterogeneity in reporting of data also limited the ability to examine the cumulative predictive properties of factors such as subthreshold manic symptoms. Among the sources of heterogeneity, differences in the baseline sample characteristics could be explored in the analyses of rates but not among that of predictors. Pooling of *OR*s for predictors with different lengths of follow-up may introduce bias, as *OR*s were reported at different time points. However, in the absence of individual participant-level data or survival curves for most studies, this method may be considered acceptable (62). In addition, there may be a possible low risk of publication bias due to search parameters and limitations (e.g. limitation of studies to those published in English language).

Relevance for pre-onset identification and interventions

Given a greater clustering of transition to BD in the first few years in individual studies and meta-analysis, follow-up and prevention efforts may be more effective in this time period. The value of combining risk factors in risk prediction approaches is suggested by an additive effect of predictive variables (48, 63), though this was not able to be explored in the meta-analytic component. Depressed persons who have an earlier onset, a family history of BD, comorbid psychotic symptoms and/or subthreshold manic symptoms may be the most appropriate target group for EI. Alternately, this may have direct clinical relevance in considering the risks of transition for adults and youth presenting with depressive episodes in routine clinical care. Earlier interventions in such populations should consider the risk-benefit profiles of such interventions and thus less specific, but more benign interventions may be preferable in such earlier stages (64, 65). Consideration of diagnosis for such individuals may also be conceived in a cross-diagnostic staging perspective where such episodes of major depression may be considered to be at a pre-illness stage for a more severe stage of recurrent unipolar disorder or a different disorder such as BD or psychotic disorders.

Considering outcomes broader than BD, such as severe psychotic disorders in a trans-diagnostic prevention approach may be useful as some of these risk markers may be true for severe psychotic disorders as well. Future meta-analyses using trans-diagnostic outcomes or primary cohort studies of young people enriched using these risk factors may assist in refining risk stages for BD and psychoses. Given that MDD may herald the onset of a range of serious

mental illnesses, as well as poor physical health and vocational outcomes, including multiple outcomes in prevention strategies is not only helpful but may even be necessary as statistical power may be limited in efforts for single disorder prevention (66).

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Fig 1: Flow diagram of studies selected for inclusion

Records identified through database searching (n = 5531)	Additional records identified through other sources (n = 23)

Records screened (n = 5554) → Records excluded (n =5366)

Full-text articles assessed for eligibility (n = 188)

Full-text articles excluded (n= 133) (n= 36, BD outcomes not assessed or reported n= 23, mixed diagnostic samples n =17 diagnosis does not meet inclusion standard n= 17 sample analyzed cross-sectionally n = 7 data not available despite communication with author. E.g. conference abstracts n =6 sample analyzed as pooled affective disorders n= 9 chart based n=9, registry-linkage, n = 6 reviews, n=2, inadequate length of follow-up)

Studies included in qualitative synthesis (n = 56)

Studies included in quantitative synthesis

Studies included in quantitative or qualitative synthesis of predictors (n =24)

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Study name		Statistics for each study					Rate and 95% CI
	Rate	Standard error	Variance	Lower limit	Upper limit		
Kane 82	0.046	0.046	0.002	-0.044	0.135		
Prien 84	0.069	0.016	0.000	0.038	0.099		
Coryell 87	0.035	0.007	0.000	0.021	0.049		
Johnson 91	0.031	0.007	0.000	0.017	0.045		
Strober 93	0.043	0.019	0.000	0.005	0.082		
Bauwens 98	0.020	0.029	0.001	-0.036	0.077		
Schwartz 2000	0.035	0.013	0.000	0.009	0.061		
Furukawa 2000	0.028	0.013	0.000	0.003	0.053		
Delbello 03	0.081	0.018	0.000	0.047	0.116		
Benvenuti 08	0.034	0.012	0.000	0.010	0.058		
Sharma 14	0.057	0.023	0.001	0.011	0.102		
	0.040	0.005	0.000	0.030	0.049		

-0.25   -0.13   0.00   0.13   0.25

Fig 2: Incidence of BD in the first 2 years of follow-up in random effects meta-analysis (n=11). Sensitivity analysis excluding Gan 11 due to high statistical ($I^2 = 49.5\%$) and clinical heterogeneity. Heterogeneity for current analysis (Q= 10.46, df= 10, $I^2 = 4.4\%$)
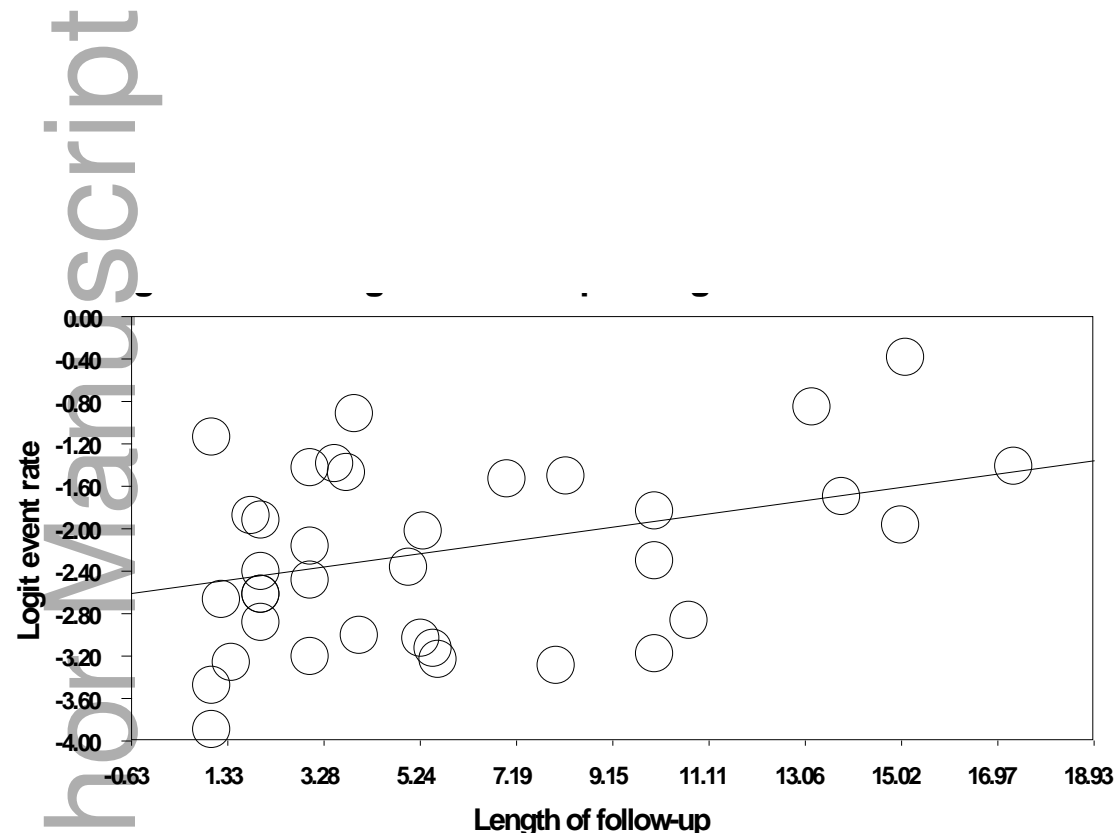
Figure 3: Metaregression of point prevalence of bipolar disorder on length of follow-up (n= 34 independent reports Slope 0.062, SE= 0.03, p= 0.038, $T^2 = 0.62$).

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Comparison	Study name	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Antidepressant Use	Goldberg 01	2.500	0.976	6.404	
Antidepressant Use	Delbello 03	0.584	0.193	1.767	
Antidepressant Use	Benvenuti 08	3.051	0.371	25.121	
Antidepressant Use	Sharma 14	1.889	0.320	11.146	
		1.532	0.675	3.477	
Family history of BD	Goldberg 01	2.000	0.360	11.126	
Family history of BD	Sharma 14	6.737	1.144	39.667	
Family history of BD	Strober 82	4.300	1.144	16.167	
Family history of BD	Akiskal 83	28.333	3.542	226.637	
Family history of BD	Ruggero 11	1.247	0.227	6.842	
Family history of BD	Fiedorowicz 11	2.426	1.363	4.319	
Family history of BD	Tondo 14	2.719	2.088	3.542	
		2.885	2.012	4.136	
Family history of depressive disorders	Ruggero 11	4.263	1.159	15.679	
Family history of depressive disorders	Fiedorowicz 11	0.938	0.616	1.429	
Family history of depressive disorders	Boschloo 14	1.367	0.644	2.901	
		1.418	0.711	2.828	
Family history of mood disorders	Strober 82	4.086	0.479	34.859	
Family history of mood disorders	Tondo 14	1.612	1.301	1.996	
Family history of mood disorders	Li 14	1.400	0.285	6.882	
Family history of mood disorders	Paaren 14	3.240	0.952	11.025	
		1.655	1.344	2.038	
Female gender	Goldberg 01	0.944	0.365	2.441	
Female gender	Akiskal 83	0.647	0.258	1.622	
Female gender	Ruggero 11	1.046	0.311	3.515	
Female gender	Fiedorowicz 11	1.418	0.906	2.222	
Female gender	Tondo 14	0.691	0.570	0.837	
Female gender	Li 14	0.841	0.304	2.331	
Female gender	Boschloo 14	0.260	0.138	0.488	
		0.737	0.480	1.130	
Psychotic symptoms	Goldberg 01	7.636	1.492	39.096	
Psychotic symptoms	Strober 82	45.000	7.796	259.747	
Psychotic symptoms	Akiskal 83	4.132	1.423	11.996	
Psychotic symptoms	Johnson 91	1.087	0.310	3.807	
Psychotic symptoms	Coryell 95	3.287	1.395	7.741	
		4.760	1.789	12.664	

0.01   0.1   1   10   100

Lower odds with risk factor present   **Higher odds with risk factor present**
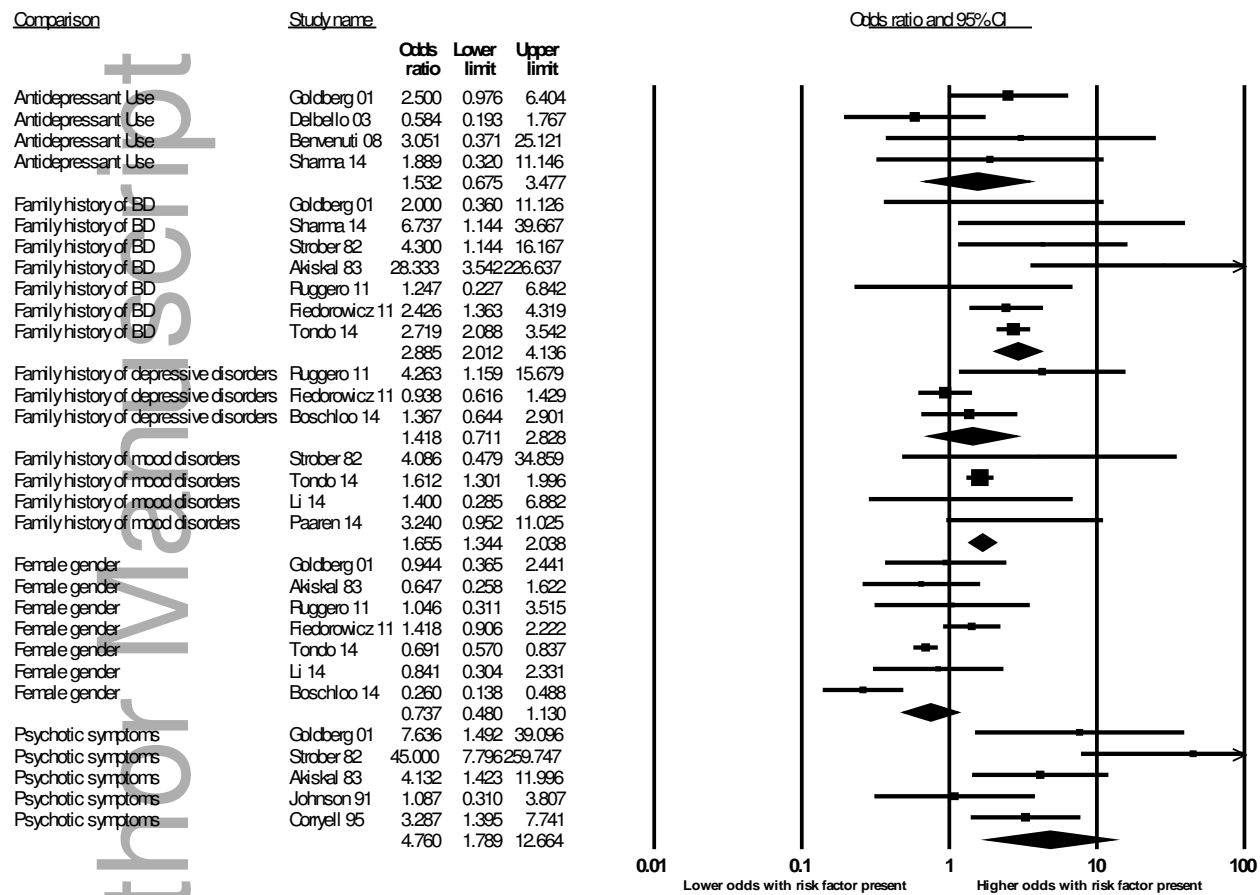
Fig 4: Categorical predictors of transition to Bipolar Disorder (BD) in random effects meta analyses

Note: Heterogeneity values are as follows: Antidepressant use (Q=2.62, Q df=3, I^2=0%), Family history of BD (Q=6.93, Q df=6, I^2= 13.4%), family history of mood disorders (Q=1.94, Q df=3, I^2= 0%), family history of depressive disorders (Q=2.49, Q df=2, I^2=19.7%), female gender (Q=5.84, Q df=6, I^2= 0%), presence of psychotic symptoms (Q=5.29, Q df=4, I^2= 23.5%)

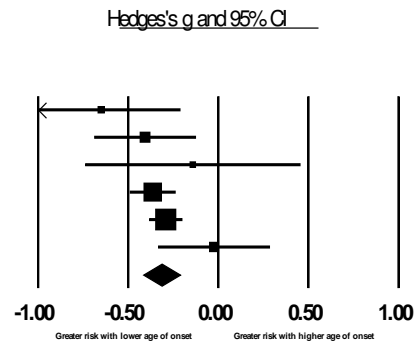| Study name	Statistics for each study					Hedges's g and 95% CI
	Hedges's g	Standard error	Variance	Lower limit	Upper limit	
Akiskal 83	-0.650	0.225	0.050	-1.090	-0.209	
Coryell 95	-0.407	0.144	0.021	-0.689	-0.124	
Ruggero 11	-0.141	0.305	0.093	-0.739	0.457	
Gilman 12	-0.364	0.065	0.004	-0.492	-0.236	
Tondo 14	-0.292	0.047	0.002	-0.385	-0.199	
Boschloo 14	-0.024	0.159	0.025	-0.335	0.287	
	-0.316	0.052	0.003	-0.418	-0.213	

-1.00 -0.50 0.00 0.50 1.00

Greater risk with lower age of onset   Greater risk with higher age of onset

Fig 5: Impact of age of onset on transition to BD in random effects analysis (Hedges g= -0.33, *SE*=0.05, *Q*=5.90, *df*= 5, I^2=15.3%))

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